Distinct and shared functions of ALS-associated proteins TDP-43, FUS and TAF15 revealed by multisystem analyses.

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Public Summary:
RNA binding proteins bind to RNA in cells to control much of their regulation, such as splicing, stability, transport and translation. RNA binding proteins TDP-43 and FUS/TLS have been previously implicated in ALS and studied. Here we study a closely related family member TAF15 that has also been implicated in ALS. We find similarities between TAF15 and FUS/TLS, but not TDP-43 and identify RNA substrates that are bound and a new motif recognized by TAF15 in mouse brains. Using human IPSC cells from normal and ALS patients, we also identify that TAF15 and FUS affect RNA turnover and have downstream effects on targets resembling ALS FUSR521G mutants and late-stage sporadic ALS patients.

Scientific Abstract:
The RNA-binding protein (RBP) TAF15 is implicated in amyotrophic lateral sclerosis (ALS). To compare TAF15 function to that of two ALS-associated RBPs, FUS and TDP-43, we integrate CLIP-seq and RNA Bind-N-Seq technologies, and show that TAF15 binds to approximately 4,900 RNAs enriched for GGUA motifs in adult mouse brains. TAF15 and FUS exhibit similar binding patterns in introns, are enriched in 3' untranslated regions and alter genes distinct from TDP-43. However, unlike FUS and TDP-43, TAF15 has a minimal role in alternative splicing. In human neural progenitors, TAF15 and FUS affect turnover of their RNA targets. In human stem cell-derived motor neurons, the RNA profile associated with concomitant loss of both TAF15 and FUS resembles that observed in the presence of the ALS-associated mutation FUS R521G, but contrasts with late-stage sporadic ALS patients. Taken together, our findings reveal convergent and divergent roles for FUS, TAF15 and TDP-43 in RNA metabolism.